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NOVARTIS

November 28, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm 1061
Rockville, MD 20852

Subject: Response to Draft Guidance for Industry: Analytical Procedures and Methods Validation, (Federal Register, Wednesday, August 30, 2000, Docket # 00D-1424)

To Whom It May Concern:

Novartis Pharmaceuticals Corporation has reviewed the draft guidance and has the following comments:

Please find enclosed in tabular format a compilation of comments, and or observations from Novartis Pharmaceuticals Corporation, East Hanover, NJ and Novartis Pharma. AG, Basle, Switzerland, on the above cited draft guidance to industry.

Please also note that Novartis also has the following general comments concerning the proposed draft guidance:

Firstly, this draft guidance deals with two distinct topics: The concepts related to analytical method validation and documentation/sample requirements to fulfill FDA analytical laboratory method "validation" efforts. It would be useful to divide the topics into two Guidance documents.
Additionally, the word "validation" is used in two contexts: to describe the process by which an analytical method is shown to be accurate, linear, precise, etc. and to describe the unrelated concept of double-checking the sponsor's analytical methods in an FDA laboratory. We recommend that the term method "verification" be used to describe the FDA analytical laboratory efforts, and that the term method "validation" be reserved for the activities surrounding proof of the analytical method's accuracy, linearity, etc.

Secondly, the requirement for submission of three copies of the method validation (verification) data package is retained in this draft. We recommend that only a single copy be submitted with the NDA/ANDA application, and the remaining two copies be forwarded to the FDA labs at the time that samples are requested. Frequently, during NDA review, a change is made and it becomes necessary to provide updated method validation (verification) packages. In this case, it is burdensome to provide triplicate copies of a section of the dossier that may not be used.

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Thirdly, the draft guidance requests a new category of data to be provided—stress data on drug substance, drug product and excipients in the analytical reagents used for evaluation (Part VII.A.2.b). The outcome of this extensive analytical effort will yield misleading, irrelevant or uninterpretable analytical data that are artefacts of the stress studies and not representative of interactions likely to occur. As these data would not be relevant to product stability (tested according to ICH conditions) nor to analytical method validation (performed under specified conditions), the value of these data are questionable.

Finally, multiple requests for raw data to be included in various portions of the Application appear to overlap with the data examination that occurs at the sponsor's facilities during a pre-approval inspection (PAI), and should be clarified.

Thank you for the opportunity to comment. If you have any questions, please contact me at (973) 781-7005.

Sincerely,

Robert J. Clark
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

Enclosures: Comments provided in duplicate

Line specific comments follow.

Lines	Comments
26	we recommend cross-referencing the term "drug substance" with the term "API (active pharmaceutical ingredient)" for consistency with other guidances
lines 89-92	Delete the first sentence. All analytical procedures are not validated to the same degree, but this is not saying that each procedure by itself is not important. This sentence doesn't add to the document - the next sentence suffices. Reword the last sentence: "Each quantitative analytical procedure should be designed so that the variability supports the intended specification limits.
lines 116-118	Reword: "If an alternative analytical procedure is submitted, the applicant should provide a rationale for its inclusion, identify its use (e.g., release, stability testing), and supply validation data as well as data comparing the alternative method to the regulatory procedure."
line 136	Is Pharmacopoeia Europa considered an official source of reference standards as well as USP?
line 149	What exactly is expected for proof of suitability of a reference standard from an official source?
line 279	Reword: "Chromatographic analytical procedures should include system suitability testing and criteria where appropriate." [Note that TLC tests used only for Identification should not need a system suitability test.]
line 283	Reword: "System suitability testing is recommended as a component of any instrumental analytical procedure...".
line 286	Delete the last sentence in this paragraph. Although a blank titration may be useful in diagnosing problems, it is not a system suitability test
lines 323-325	We question the need to state the detection limit DL and quantitation limit QL in the method description, as this information is contained within the analytical method validation. This approach is more consistent with ICH. We note also that a cross-reference to the terms "limit of detection LOD" and "limit of quantitation LOQ" might also be useful. In addition, the type of impurity tested for—degradation product, by product, etc.—is not particularly relevant to the analytical procedure being validated.
line 326-327	Change sentence to read: "The detection limit (DL) or quantitation limit (QL) should be stated or the reporting level should be justified, as appropriate."
line 333	Change sentence to read: "...sum of all impurities equal or greater than their individual reporting levels." The true quantitation limit may be well below the required reporting levels.
line 373	Add Selectivity, i.e. Specificity/Selectivity. [Note that although Specificity is the term commonly used, Selectivity is usually more appropriate. The former implies that there are no other components of a sample that an analytical procedure will "respond to", while the latter implies that, although other components may be present and detectable by the methodology used, the response is so low that the level of interference is insignificant.]
line 385	Add "... and subsequent investigations, if necessary."
line 387	Suggest rewording: "Legible reproductions of representative instrument output or recordings (e.g., chromatograms). Instrument output for placebo, standard and sample must also be provided..."
lines 392-93	Delete this sentence. Providing calculations for actual samples in the method

	validation report has no value. {Note that this can be part of the sample submission package to FDA.]
lines 402-415	Information on impurities, actual or theoretical, is more appropriately provided in the impurity section of drug substance characterization, unless these compounds form solely during the analytical procedures. If general information for the FDA laboratory chemist is desired, perhaps only the structure list from lines 414-415 could be provided in the method verification data package with the verification samples.
lines 441-448	The wording of this paragraph suggests that the applicant must perform whole product degradation studies with the various reagents listed. Degradation (stress) studies should be performed with the API (to determine the degradation profile) and with the formulation excipients (placebo) to demonstrate that degradation products of excipients would not interfere with the quantitation of the API or known degradation products of the API. Potential reactions of the API with formulation excipients are evaluated with excipient compatibility studies and stability studies (supportive) are performed during early development activities. Generally there is no need to stress the drug product with the reagents listed. Additionally, these types of stress studies may predict API degradation products which would never occur under real life storage conditions. If the result of these studies is experimental artefacts unrelated to ICH stability studies and challenges to analytical validation, they present limited real-life information or added value.
lines 450-453	Neither the design of nor the data from the stress studies (with reagents) should be part of the stability section of the application, as the stability section of the NDA/ANDA contains information supporting shelf life of the commercial image formulation in the intended commercial container system. Any product degradation/reagent study information (including data output, e.g., chromatograms) should be included in the method validation report, *if it is included in the final Guidance* (see comments above).
lines 460-461	Representative data for residual solvents (OVIs) needs to be included in the method validation report to support the ranges chosen for the linearity and accuracy (recovery) experiments. However, there should not be a requirement to include raw numerical values (e.g., peak area), as they are not meaningful for calculation purposes unless other parameters are also (standard and sample weights, etc). Please clarify the purpose of this data request.
line 464	The level of one or more known impurities in a sample may be significantly greater than the LOQ under routine conditions. Please clarify how one assesses the impurity profile at the quantitation limit for this case?
lines466-469	Please delete this sentence as too specific, or provide a more general example.
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lines 498-504	The utility of raw data references in the Stability section of the Application is unclear. As noted in comments to lines 450-453 above, the purpose of the Stability section of the Application is not to evaluate the methods used to obtain the stability data. Further, all raw stability analytical data is available to FDA investigators at the time of a pre-approval inspection (PAI) and it is our understanding that review of this raw data is within the role of the investigator. The need to capture this information in the Application as well is questionable.
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line 586	The stability of all standard solutions needs to be determined as well.
lines 605-608	Delete this paragraph. There should not be a requirement to supply raw data from methods validation in the application. This information is available to the FDA investigator during the PAI Additionally, raw data on the test batch are provided to the FDA analytical laboratory as part of the method verification sample package.
lines 630-637	The possibility of transfer of a validated method to another testing laboratory (e.g. related to a site change of manufacture) is not considered.
line 652 and following section	Please rename as the Method Verification or Method Evaluation Data Package to distinguish the FDA lab activities from the sponsor's method validation activities. This may also be presented as a separate guidance. Please reconsider the need to provide triplicate copies of this section with the original Application.
line 668	Clearly identify the samples to be provided (drug substance, standards, drug product).
line 779	Change to "verified" or "evaluated"
line 805	In the guidance document the "P" of HPLC stands for **Pressure** in accordance with the original definition when this technique was first developed. Meanwhile many experts in the field of chromatography have identified "pressure" as a negative factor influencing the separations (e.g. sudden pressure surges and mechanical shocks should be avoided; voids can also develop as a result of pressure surges). As a consequence "P" in HPLC is nowadays more often associated with **P**erformance than with pressure. Suggest adopting this more modern definition.
line 823	Delete frit size as this is normally part of vendor specification
line 826	Add "column temperature, if applicable"
Lines 830-832	Delete as these are normally part of vendor specification
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lines 860-871	The operating parameters injection volume, detector, typical retention times, total run time are not considered. Is a discussion of these not expected?
line 863	Change to "...and samples should be defined, if necessary." A suggested injection sequence should not be included in a method as routine practice; this should be reserved for those cases where it adds value to a method (i.e., affects the outcome of the method)

lines 867-868	Details such as order of addition of reagents and method of degassing should only be provided in situations where they can affect the outcome of the analysis.
line 886	Change to "Column conditioning procedure, if necessary (Note: This is generally detailed in the technical literature supplied by the Column Vendor. This information should only be included if it is different from this procedure, or if the column needs to be "loaded" prior to collection of data.)
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EAST HANOVER NJ 07936
973-781-8769

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ACTUAL WGT: 0.60 LBS

Part # 156148 RMT 08-0C

TO:

973-781-3817

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FOOD AND DRUG ADMIN (HFA-305)
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